Pediatric Neuromuscular Disorders: Transitions to Adult Providers

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Disclosures

• Advisory board for Sarepta Therapeutics and Marathon Pharmaceuticals

• Active clinical trials: PTC Therapeutics, Eli Lilly, Sarepta Therapeutics, Pfizer, and Marathon Pharmaceuticals

• Funding from MDA, NIH, CureCMD
Objective

• Duchenne muscular dystrophy— as a model for other neuromuscular disorders
  – Clinical and genetic features of DMD
  – Brief introduction to some common neuromuscular disorders presenting in childhood
  – Successes in treatment and change in natural history
  – Challenges of adult patients with a pediatric disease
MDA clinic patients Feb/March 2013
Duchenne Muscular Dystrophy

• Patients come to medical attention between 3 to 5 yrs due to gait abnormalities
  – Clumsiness, toe walking, not keeping up with peers
• Calf pseudohypertrophy
• Weakness: Proximal > Distal
  – Gower sign
• CK markedly elevated (10-20,000)
  – Elevation even in pre-symptomatic patient
• Genetic mutation in DMD gene identified in 98%
  – Out-of-frame deletions
  – Nonsense (stop) mutation
Clinical Features

• Musculoskeletal:
  – Contractures: ankles, hips, and knees etc.
  – Scoliosis

• Respiratory insufficiency
  – progressive especially after loss of ambulation

• Cardiomyopathy
  – Dilated; Especially > 15 years
  – Increasing mortality due to cardiomyopathy

• Cognitive difficulties in 1/3 of patients
  – Generally language, behavioral
  – Mean IQ ~ 88
Becker Muscular Dystrophy

• Mutation in *DMD* gene is milder
  – Residual expression of dystrophin
  – Missense or in-frame

• Similar symptoms to DMD but later onset
  – Early adolescence or young adulthood

• Variable rate of progression
  – Most ambulatory into 30’s or 40’s
Spinal Muscular Atrophy  
SMA

- Degeneration of lower motor neuron
- Weakness, hypotonia
  - Proximal > distal
  - Facial expression often preserved
- Normal cognitive development
  - May mask progressive muscle weakness
- Respiratory involvement
  - Weak diaphragm, chest wall muscles
- Subtypes clinically defined
  - Type 1 onset <6m, death in first two years
    - Never sits without support
  - Type 2 onset 6-18m
    - May sit independently, but never walks
  - Type 3 onset >18m
    - Walks independently (at least 25m)
    - Ambulate into adulthood
Myotonic Dystrophy

- CTG expansion in *DMPK*
- Typical onset in late childhood, early adolescence
- Clinical features
  - Percussion myotonia
  - Handshake
  - Bi-temporal narrowing
  - Fish-shaped mouth
    - Myopathic facies
  - Atrophy of forearms

Images from wustl neuromuscular webpage and Jorde et al. *Medical Genetics 2nd ed.*
Facioscapulohumeral Dystrophy
FSHD

• Weakness—may be asymmetric
  – Facial muscles
  – Stabilizers of the scapula (scapular winging)
  – Biceps/triceps
  – Peroneal
    • Dorsiflexion and eversion of foot

• Onset in adolescence

• Severity highly variable even within families

• Slowly progressive
  – 20% eventually require a wheelchair
Limb-Girdle Muscular Dystrophy
LGMD

- Proximal>distal weakness
- CK elevation
- Dystrophic biopsy
- Adult or adolescent onset:
  - Calpain (LGMD2A)
  - Dysferlin (LGMD2B)
  - Onset may be subtle
  - May be several years before care is sought
- Childhood onset
  - Sarcoglycan (LGMD2C, 2D, 2E)
  - Similar onset/progression to DMD
From DMD standard of care guidelines. *Lancet Neurology* 2009. Issues are similar in all NMD
Changing Natural History

• Daily oral corticosteroid from age 5
  – Patients walk 2-5 years longer
    • Some with ambulation into early teens
  – Significant side effects from steroid
• Less need for spine stabilization surgery
• Delay in need for non-invasive ventilation
• Cardiac: preserved LVEF
• Transitions:
  – Patients are reaching adulthood with concerns for college, work, family etc.
  – Shoes
Changing Natural History

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N = 27)</th>
<th>Group 2 (N = 13)</th>
<th>Group 3 (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at loss of ambulation</td>
<td>9.6</td>
<td>8.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Mean age ventilated</td>
<td>17.4</td>
<td>18.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Median age of survival</td>
<td>30</td>
<td>22.2</td>
<td>17.1</td>
</tr>
<tr>
<td>% survival to 20 years</td>
<td>96</td>
<td>69.2</td>
<td>25.7</td>
</tr>
<tr>
<td>% survival to 24 years</td>
<td>84</td>
<td>34.6</td>
<td>10.7</td>
</tr>
<tr>
<td>% survival to 32 years</td>
<td>26.5</td>
<td>17.3</td>
<td>3.57</td>
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INCREASING SURVIVAL IN PATIENTS WITH DMD

_Eagle M et al. Neuromuscular Disorders_

University of Rochester NMD Center

Corticosteroids and Pulmonary Management

Current Cohort
n=42
age 24.7 Yrs.
(18.2-33.6)
Died N=27
age 22.5 Yrs.
(11.2-30.9)

CHANGE OVER DECADES

Future in DMD

• First drug approved (EMA not FDA) for treatment of DMD May 2014
  – Ataluren
    • Clinically available as of December 2014 in Germany
    • Only treats patients with Nonsense mutation

• Phase 3 trials ongoing now in Utah
  – Ataluren (nonsense readthrough)
  – Exon skipping
  – Tadalafil
  – Myostatin inhibition
Transitions to Adult Care

- DMD somewhat unique
  - dramatic change in natural history surrounding age of transition

- MDA transitions project
  - Independence
  - Education
  - Career Center
  - Webinars
  - Blogs

- Issues at transition vary by diagnosis
- Similar issues by stage of disease
Natural History and Transition to Adulthood

<table>
<thead>
<tr>
<th>Stage 1: Presymptomatic</th>
<th>Stage 2: Early ambulatory</th>
<th>Stage 3: Late ambulatory</th>
<th>Stage 4: Early non-ambulatory</th>
<th>Stage 5: Late non-ambulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be diagnosed at this stage if creatine kinase found to be raised or if positive family history</td>
<td>Gowers’ sign</td>
<td>Increasingly laboured gait</td>
<td>Might be able to self propel for some time</td>
<td>Upper limb function and postural maintenance is increasingly limited</td>
</tr>
<tr>
<td>Might show developmental delay but no gait disturbance</td>
<td>Waddling gait</td>
<td>Losing ability to climb stairs and rise from floor</td>
<td>Able to maintain posture</td>
<td></td>
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<tr>
<td>Can climb stairs</td>
<td>Might be toe walking</td>
<td>Might develop scoliosis</td>
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*Stages based on DMD standard of care guidelines *Lancet Neurology* 2009

<table>
<thead>
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<tbody>
<tr>
<td>DMD</td>
</tr>
<tr>
<td>BMD</td>
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<tr>
<td>SMA type 2</td>
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<tr>
<td>SMA type 3</td>
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<tr>
<td>Myotonic</td>
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<td>FSHD</td>
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Difficulties in Transitions to Adult Care

- **Change in care model**
  - Family centered care, largely parent driven
  - Individual care

- **Social isolation**
  - Most DMD patients are satisfied with social interaction in high school years
  - After graduation patients become more isolated
    - Primary interactions with family members

- **Employment/Education**
  - Increasing numbers seeking higher education
  - Few are employed

- **End-of-life decision making**
  - Legal and ethical questions
How would you answer someone’s question as to whether it makes sense to extend life artificially to this extent? Should we think of the application of VAD technology any differently than we do mechanical ventilation?

Summarized comment From Palliative care provider at Cincinnati:

Considerations in use of LVAD in DMD patient:
(complex) mother-patient relationship,
the family-patient relationship—determining the family's goals in receiving a VAD
Is it truly the patient's wishes to undergo this procedure?
Who is driving this request and why?
Questions